

Submitted by:
Ye Chan Yoon, Pharm.D.
Medical Affairs
Samsung Bioepis Co., Ltd.
107, Cheomdan-daero, Yeonsu-gu,
Incheon, Republic of Korea 21987
Phone: 82-32-455-6114
Email: med.info@samsung.com
Date of request: Aug 02, 2019
NCCN Guidelines Panel: Esophageal/Gastric Cancer

On behalf of Samsung Bioepis, I respectfully request the NCCN Esophageal/Gastric Cancer Guideline Panel to review the enclosed data for inclusion of Ontruzant® (trastuzumab-dttb), a biosimilar of Herceptin® (trastuzumab), for the treatment of patients with HER2-positive metastatic gastric or gastroesophageal junction adenocarcinoma.

Specific Changes: Recommend the addition of Ontruzant® as a treatment option for patients with HER2-positive metastatic gastric or gastroesophageal junction adenocarcinoma, similar to Herceptin®.

FDA Clearance: On Jan 18, 2019, FDA approved Ontruzant®, a biosimilar of Herceptin®, for all indications of Herceptin, including the treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

Rationale: The FDA approved Ontruzant® as a biosimilar to Herceptin® based on the totality of the evidence in accordance with the FDA 351(k) pathway. The development program for Ontruzant® demonstrated that Ontruzant® is highly similar to Herceptin®, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between Ontruzant® and Herceptin® in terms of safety, purity, and potency. Ontruzant® may provide an alternative treatment option and allow better access to biologics for patients.

Analytical Tests and Non-clinical studies

The extensive comparison of structural, physicochemical and biological properties demonstrated that Ontruzant® is similar to Herceptin®.

Clinical Pharmacology

In SB3-G11-NHV (randomized, double-blind, three-arm, parallel group, and single-dose study in healthy male subjects; NCT02075073), the ratios (90% CI) of geometric means for primary pharmacokinetics (PK) endpoints (AUC_{0-12h} , $AUC_{0-\infty}$, and C_{max}) were all within the pre-defined equivalence margin (0.8 to 1.25), demonstrating PK equivalence between Ontruzant® and Herceptin®.

In SB3-G31-BC (randomized, double-blind, parallel group, and multicenter study; NCT02149524), the mean serum concentration after drug administration was similar between Ontruzant® and Herceptin® from Cycles 3 to 8, providing supportive PK data from breast cancer patients.

Immunogenicity

In SB3-G11-NHV, no subject developed anti-drug antibodies in any treatment groups. In addition, the phase III study (SB3-G31-BC) demonstrated that the overall incidence of anti-drug antibody was low and comparable between Ontruzant® and Herceptin®.

Clinical Efficacy

The phase III study (SB3-G31-BC) demonstrated equivalence between Ontruzant® and Herceptin® in patients with HER2-positive early or locally advanced breast cancer in the neoadjuvant setting. The results showed that breast pathologic complete response (bpCR) rates were 51.7% for Ontruzant® and 42.0% with Herceptin®. The adjusted ratio of bpCR was 1.259 (90% CI, 1.112 to 1.426), which was within the predefined equivalence margin (0.785, 1.546). After completion of adjuvant period, treatment-free follow-up is planned for a total of 5 years to evaluate long-term cardiac safety and survival outcome (NCT02771795). The 3-year follow-up results are enclosed for

your consideration.

Clinical Safety

The phase I study (SB3-G11-NHV) demonstrated that the safety profiles were similar between Ontruzant® and US-Herceptin®. The majority of treatment-emergent adverse events (TEAEs) were Grade 1 (mild) or Grade 2 (moderate) in severity.

The phase III study (SB3-G31-BC) demonstrated that the safety profiles between Ontruzant® and Herceptin® were similar in patients with HER2-positive early and locally advanced breast cancer. The overall incidences of TEAEs and severity of reported TEAEs were comparable between Ontruzant® and Herceptin® up to 1-year.

Extrapolation

Trastuzumab's mechanism of action and the target receptor involved are the same across all indications. The dose and the route of administration of Herceptin® is the same across all indications. The consistent mechanism of action of trastuzumab combined with the results from the analytical studies, the preclinical studies, and the PK and Phase III comparability studies, as well as the safety and immunogenicity profile of Ontruzant® supports extrapolation to all indications of the reference product.

The following articles are submitted in support of this proposed change.

1. Ontruzant (trastuzumab-dttb). Full Prescribing Information, Merck Sharp & Dohme Corp., White House Station, NJ, USA, 2019.
2. Lee, J.H., Paek, K., Moon, J.H. et al. Biological characterization of SB3, a trastuzumab biosimilar, and the influence of changes in reference product characteristics on the similarity assessment. *BioDrugs* (2019). <https://doi.org/10.1007/s40259-019-00362-5>
3. Pivot X, Curtit E, Lee YJ, et al. A randomized phase I pharmacokinetic study comparing biosimilar candidate SB3 and trastuzumab in healthy male subjects. *Clin Ther* 2016; 38(7): 1665-1673 e3.
4. Pivot X, Bondarenko I, Nowecki Z, et al. Phase III, randomized, double-blind study comparing the efficacy, safety, and immunogenicity of SB3 (trastuzumab biosimilar) and reference trastuzumab in patients treated with neoadjuvant therapy for human epidermal growth factor receptor 2-positive early breast cancer. *J Clin Oncol* 2018; 36: 968-74.
5. Pivot X, Bondarenko I, Nowecki Z, et al. A phase III study comparing SB3 (a proposed trastuzumab biosimilar) and trastuzumab reference product in HER2-positive early breast cancer treated with neoadjuvant-adjuvant treatment: Final safety, immunogenicity and survival results. *Eur J Cancer* 2018; 93: 19-27.
6. Pivot X, Pegram MD, Cortes J, et al. 3-year follow-up of a phase III study comparing SB3 (trastuzumab biosimilar) and reference trastuzumab in HER2 positive early or locally advanced breast cancer in neoadjuvant setting. Presented at: St Gallen International Breast Cancer Conference 2019; March 20-23, 2019; Vienna, Austria. Abstract P150.
7. Pivot X, Pegram MD, Cortes J, et al. Evaluation of survival by ADCC status: Subgroup analysis of SB3 (Trastuzumab Biosimilar) and reference trastuzumab in patients with HER2-positive early breast cancer at three-year follow-up. Presented at: the American Society of Clinical Oncology Annual Meeting 2019; May 31-June 4, 2019; Chicago, Illinois. Abstract 580.
8. FDA. Scientific considerations in demonstrating biosimilarity to a reference product: Guidance for industry.

We appreciate your consideration of Ontruzant® for inclusion in the NCCN Gastric Cancer, and Esophageal and Esophagogastric Junction Cancers Guidelines, similar to Herceptin®. If you have any questions, please contact me at med.info@samsung.com.

Sincerely,

Ye Chan Yoon, PharmD
Medical Affairs
Samsung Bioepis Co., Ltd.